

DOCKET NO.: 206269US0PCT



IN THE UNITED STATES PATENT & TRADEMARK OFFICE

#17
6/9/03
J. Meier

IN RE APPLICATION OF:

SHIGERU KAWAHARA ET AL

: EXAMINER: ZUCKER

SERIAL NO. : 09/830,159

FILED: JUNE 27, 2001

: GROUP ART UNIT: 1621

FOR: CRYSTALLIZATION
PROCESSES FOR THE
FORMATION OF STABLE
CRYSTALS OF ASPARTAME
DERIVATIVE

RECEIVED
MAY 30 2003
TECH CENTER 1600/2900

RESPONSE AND REQUEST FOR RECONSIDERATION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VA 22313

SIR:

In response to the Advisory Action dated April 11, 2003, Applicants respectfully request reconsideration of the above-identified application in view of the following remarks.

REMARKS

In the Advisory Action dated April 11, 2003, the Examiner indicated that the second declaration of Kawahara had not been considered because it was not executed. Accordingly, Applicants are filing herewith the second declaration of Kawahara in executed form. Applicants respectfully submit that the second declaration of Kawahara should now be

considered and that the claims of the present application are patentable for the reasons set forth in the Response and Request for Reconsideration filed on March 26, 2003.

Applicants submit that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618



22850

A handwritten signature in black ink, appearing to read 'Stephen G. Baxter'.

Stephen G. Baxter, Ph.D.
Registration No. 32,884

(703) 413-3000
Fax #: (703) 413-2220
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DECLARATION UNDER 37 C.F.R. § 1.132

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Now comes Shigeru Kawahara, who deposes and states:

1. That I am a named inventor of the above-identified application.
2. That I received my degree in chemistry from Tokyo Institute of Technology in 1998.
3. That I have been employed by Ajinomoto Company, Inc., the assignee of the above-identified application for 5 years as a chemist in the field of process chemistry.
4. That I am the same Shigeru Kawahara who executed a first declaration under 37 C.F.R. § 1.132 in this application on July 19, 2002.
5. Even in the same material, several kinds of crystalline states (crystal forms) can exist. X-ray powder diffraction (XRPD) has long been used to identify and characterize

crystalline powders. In order to discriminate between crystalline powder samples which commonly contain the same material but belong to the different crystal forms, XRPD is the most powerful and convenient method. The XRPD patterns of the same materials belonging to different crystal forms demonstrate diffraction peaks with different 2θ angles.

6. It is a conventional identification method for a specific crystal to find crystal(s) having the same three strongest peaks of the specific crystal on XRPD data bases and, when found, to analyze coincidence of other peaks between them. In general cases, a crystal can be identified when the strongest eight peaks are coincident. In the case of the specific crystals of a particular compound, for instance, A-type crystals, B-type crystals, or other types crystals of Neotame, it is possible to identify any one of them by using one strong and characteristic peak, as the case may be.

7. The identification of crystal types by XRPD (or by several characteristic or specific diffraction peaks obtained therein) is well accepted by those who are skilled in the art, as a means for the identification of crystal types. For example, in U.S. Patent No. 4,579,747, which issued on April 1, 1986, two types of Aspartame crystals (IIA and IIB) were claimed by identification of four (4) diffraction peaks. In U.S. Patent No. 4,950,780, which issued on August 21, 1990, a novel crystalline structure of n-octadecyl-3-(3,5-di-t-butyl-4-hydroxyphenyl)-propionate was claimed by the identification of only one (1) diffraction peak. In European Patent No. 0 279 542 B1, granted on August 12, 1991, β -type crystals of aspartic acid were claimed in terms of only three (3) diffraction peaks.

8. As has been described above, XRPD is widely used among those skilled in the art to identify the crystal type of a compound. Peaks obtained by XRPD reflect the internal structure of the crystal concerned, and the obtained peaks are peculiar or specific to the

crystal. Therefore, for the identification of the crystal type of a given compound, not all the peaks need to be assigned, and it suffices that some typical peaks are consistent with those of an authentic sample.

9. To demonstrate that the peaks at 6.0° , 8.2° , 16.5° , and 24.8° are sufficient to identify A-type crystals of Neotame, the following experiments were carried out by me or under my direct supervision and control.

(A) First, the A-type crystals of Neotame obtained by the crystallization method of the present invention were analyzed by XRPD, and this analysis gave the chart shown in Fig.

1. The B-type crystals of Neotame obtained by repeating Example 1 of U.S. Patent No. 5,728,862 (Prakash et al) were analyzed by XRPD, and this analysis gave the chart shown Fig. 2.

(B) The diffraction pattern of the A-type crystals shown in Fig. 1 was compared with that of the B-type crystals shown in Fig. 2 as follows. First, the relatively strong peaks of the A-type crystals were assigned Nos. A1-A20, respectively, as indicated in Fig. 3 (A-type crystals), for the sake of convenience of explanation in making the comparison. The diffraction angles and relative intensity of peaks Nos. A1-A20 were collected and are listed in Table 1. Similarly, the relatively intense peaks of the B-type crystals were assigned Nos. B1-B18, respectively, as indicated in Fig. 4 (B-type crystals), and are listed in Table 2.

TABLE 1 (A-Type Crystals)

No.	<u>Diffraction angle</u>	<u>Relative intensity</u>
	2θ	$I/I_1(\%)$
A1	5.95	100
A2	8.22	28
A3	12.41	7
A4	14.21	28
A5	16.54	59
A6	16.88	24
A7	17.69	32
A8	19.80	17
A9	20.42	76
A10	20.88	22
A11	21.31	14
A12	21.92	14
A13	22.94	40
A14	23.82	23
A15	24.76	17
A16	25.00	16
A17	26.00	41
A18	26.32	32
A19	26.67	29
A20	28.69	25

TABLE 2 (B-Type Crystals)

No.	<u>Diffraction angle</u>	<u>Relative intensity</u>
	2 θ	I/I ₁ (%)
B1	5.16	100
B2	8.42	18
B3	10.24	35
B4	11.95	8
B5	14.23	3
B6	15.69	8
B7	16.36	12
B8	17.45	7
B9	18.25	25
B10	20.51	4
B11	21.10	26
B12	21.39	18
B13	21.88	14
B14	23.94	5
B15	25.30	7
B16	25.67	6
B17	26.85	5
B18	27.28	9

The following four (4) peaks were selected from Table 1 and Fig. 3 to identify the A-type crystals: 6.0° (A1), 8.2° (A2), 16.5° (A5) and 24.8° (A15) (2 θ , CuK α line). It is clear from Table 2 and Fig. 4 that none of these four peaks appear in the chart of the B-type crystals (Fig 4).

(C) To demonstrate empirically that the four peaks selected as being characteristic of the A-type crystals and the peaks characteristic of the B-type crystal are distinguishable on one chart, the B-type crystals and the A-type crystals were each separately prepared and were mixed, and the resulting mixtures were analyzed by XRPD. The A-type and B-type crystals were prepared by repeating Example 4 and Comparative Example 1, respectively, of the above-identified application. The XRPD chart of the obtained A-type crystals (moisture 34.0 wt%) and that of the obtained B-type crystals (moisture 58.7 wt%) are shown in Figs. 5 and 6, respectively.

Mixtures of the A-type crystal and the B-type crystal were prepared and analyzed, as follows:

Mixture 1: 0.80 g of the B-type crystals and 0.24 g of the A-type crystals were placed in a mortar and mixed. The mixture gave the chart of Fig. 7, when analyzed by XRPD.

Mixture 2: A mixture of 1.0 g of the B-type crystals and 0.1 g of the A-type crystals was prepared in the same manner and gave the chart of Fig. 8, when analyzed by XRPD.

As seen from Figs. 7 and 8, the four peaks A1, A2, A5, and A15 of the A-type crystals selected by the present inventors as being characteristic of the A-type crystal are clearly distinguishable from the peaks characteristic of the B-type crystal, in both Mixtures 1 and 2. It is particularly noteworthy that, in Mixture 2, the four peaks A1, A2, A5, and A15 are distinguishable on the chart of Fig. 8, notwithstanding the fact that the A-type crystals were contained in an amount of as little as about 14 % based on the B-type crystals.

(D) In view of the foregoing, it can be safely concluded that when given crystals of Neotame are analyzed by the powder diffraction X-ray method, and if the four peaks A1, A2, A5, and A15 selected by the present inventors as being characteristic of the A-type crystals are not recognized or do not appear on the chart, then the crystals do not contain the A-type crystals.

(E) Superimposition of two charts is a technique generally employed among those who are skilled in the art, for the purpose of comparison of two charts obtained by XRPD. Specifically, one chart is placed on the other such that the X axes (2θ , $\text{CuK}\alpha$ line) just overlap each other, whereby the peaks of the one chart and those of the other can be precisely and easily compared. In accordance with this technique, the chart of the A-type crystals of Neotame (Fig. 1) and that of the B-type crystals of Neotame (Fig. 2) are shown on one sheet in such an overlapping position; in Fig. 9. As seen from Fig. 9, the four peaks selected by the present inventors as being characteristic of the A-type crystal are clearly distinguishable from those characteristic of the B-type crystal, unless the A-type crystal is really mixed with the B-type crystal.

In view of the foregoing, it could be concluded that the four peaks A1, A2, A5, and A15 selected by the present inventors as being characteristic of the A-type crystals of Neotame are sufficient for the identification of the A-type crystals of Neotame.

10. The following additional experiments were also carried out by me or under my direct supervision and control.

11. Experiment I: Repetition of Example 2 of U.S. Patent No. 5,510,508 (Claude et al), with the temperature of the water bath maintained at 38-40°C during the precipitation of the Neotame. The following were introduced successively, with stirring, into a reactor

equipped with a stirrer capable of ensuring a very good transfer of gaseous hydrogen into the liquid phase: 60 cm³ of a 0.1 M aqueous solution of acetic acid, 1 g of 10 % palladium on activated carbon, 2.55 g of 3,3-dimethylbutyraldehyde, 30 cm³ of methanol, and 5 g of aspartame. After the reactor had been purged with a stream of nitrogen, the mixture was hydrogenated at a relative pressure of 1 bar (0.1 MPa) and at room temperature. The progress of the reaction was monitored by taking a crude sample and assaying the product formed by high performance liquid chromatography (HPLC). The concentration of desired product was determined by comparison with a calibration curve established beforehand. After a hydrogenation time of 2 hours, the formation of 56 % of the expected product was observed.

The reaction was then interrupted by purging the reactor with a stream of nitrogen, and the catalyst was removed by filtration with a fine filter (0.5 μm). The methanol was then removed by evaporation under vacuum, while the temperature of the water bath was maintained at 38-40°C. During the removal of methanol by evaporation under vacuum, the temperature of the mass inside the vessel was checked by a thermometer. After 3-13 minutes, an oily material was generated, and after another 1 minutes (14 minutes from starting evaporation), a white solid rapidly precipitated. At that time, the temperature of the mass inside the vessel was 23°C. The mixture was stirred for five hours at room temperature in order to complete the precipitation. The product was collected by filtration, and the resulting wet product (5.73 g, moisture 45.92 wt%) was examined by XRPD.

The X-ray diffraction chart of the Neotame crystals obtained by Experiment I was superimposed on the chart of the B-type crystals of Neotame (Fig. 2) for the purpose of comparison with the B-type crystals, as shown in Fig. 10. As can be seen from Fig. 10, the crystals of Experiment I are of the B-type, because of the appearance on the chart of peaks B1,

B2, B11, and B12 characteristic of the B-type crystals. However, new peaks X1 ($2\theta = 5.64$) and X2 ($2\theta = 8.33$) were also observed, and therefore, the crystal is probably mixed with some unknown type crystal.

Subsequently, the X-ray diffraction chart of the Neotame crystals obtained by Experiment I was superimposed on the chart of the A-type crystals of Neotame (Fig. 1) for the purpose of comparison with the A-type crystals, as indicated in Fig. 11. As can be seen from Fig. 11, none of the peaks A1, A2, A5, and A15 selected by the present inventors as being characteristic of the A-type crystals are observed on the chart of the crystals of Experiment I.

In conclusion, the crystals of Experiment I are a mixture of B-type crystals and some unknown type crystal and are not A-type crystals.

12. Experiment II: Repetition of Example 2 of Claude et al with the solvent maintained at a temperature of not lower than 30°C during solvent removal. The following were introduced successively, with stirring, into a reactor equipped with a stirrer capable of ensuring a very good transfer of gaseous hydrogen into the liquid phase; 353 cm³ of a 0.1 M aqueous solution of acetic acid, 5.88 g of 10 % palladium on activated carbon, 15.00 g of 3,3-dimethylbutyraldehyde, 177 cm³ of methanol, and 30.64 g of aspartame. After the reactor had been purged with a stream of nitrogen, the mixture was hydrogenated at a relative pressure of 1 bar (0.1 MPa) and at 30°C. The progress of the reaction was monitored by taking a crude sample and assaying the product formed by high performance liquid chromatography (HPLC). The concentration of desired product was determined by comparison with a calibration curve established beforehand. After a hydrogenation time of 19 hours, the formation of 47.7 % of the expected product was observed. The reaction was then interrupted

by purging the reactor with a stream of nitrogen, and the catalyst was removed by filtration with a fine filter ($0.5\mu\text{m}$). The catalyst was washed by methanol (10 cm^3) and water (20 cm^3), and a combined filtrate (600 cm^3) containing 18.0 g of Neotame (yield 47.5 %) was obtained. 50 cm^3 of the resulting filtrate was used for the following concentration-crystallization process.

The above filtrate containing 1.5 g of Neotame was introduced into a four-neck round-bottom flask (200 cm^3) equipped with a stirrer and a thermometer capable of measuring the temperature of the solution inside the flask. The methanol was then removed under reduced pressure (25-100 mm Hg) for 3.5 hours so that the temperature of the solution inside the flask was allowed to drop slowly to 30°C from 42°C . The nucleation did not occur during concentration, although a viscous oil was formed out of the solution.

The flask was detached and held at room temperature for about 20 minutes. The viscous oil began to change to crystals, and the temperature inside the flask was 27.6°C . The mixture was stirred for a while in order to complete the precipitation. The product was collected by filtration, and the resulting wet-product (1.74 g, moisture 31.91 wt%) was examined by XRPD.

Thus, in Experiment II, no crystals were precipitated, notwithstanding the fact that the solvent was removed by evaporation while the internal temperature of the solvent was not lower than 30°C , *i.e.*, the temperature of the solution inside the flask, over a period of 3.5 hours. It was, thus, found that as the result of the prolonged concentration time, an oily substance insoluble in water was precipitated on, and adhered to, the inside wall of the flask, and converted to crystals only when cooled down to room temperature.

According to conventional crystallization, nucleation is caused to occur from a homogeneous solution by causing a supersaturation gradually. In contrast, in Example 2 of Claude et al, an oily substance is first formed and then converted to crystals.

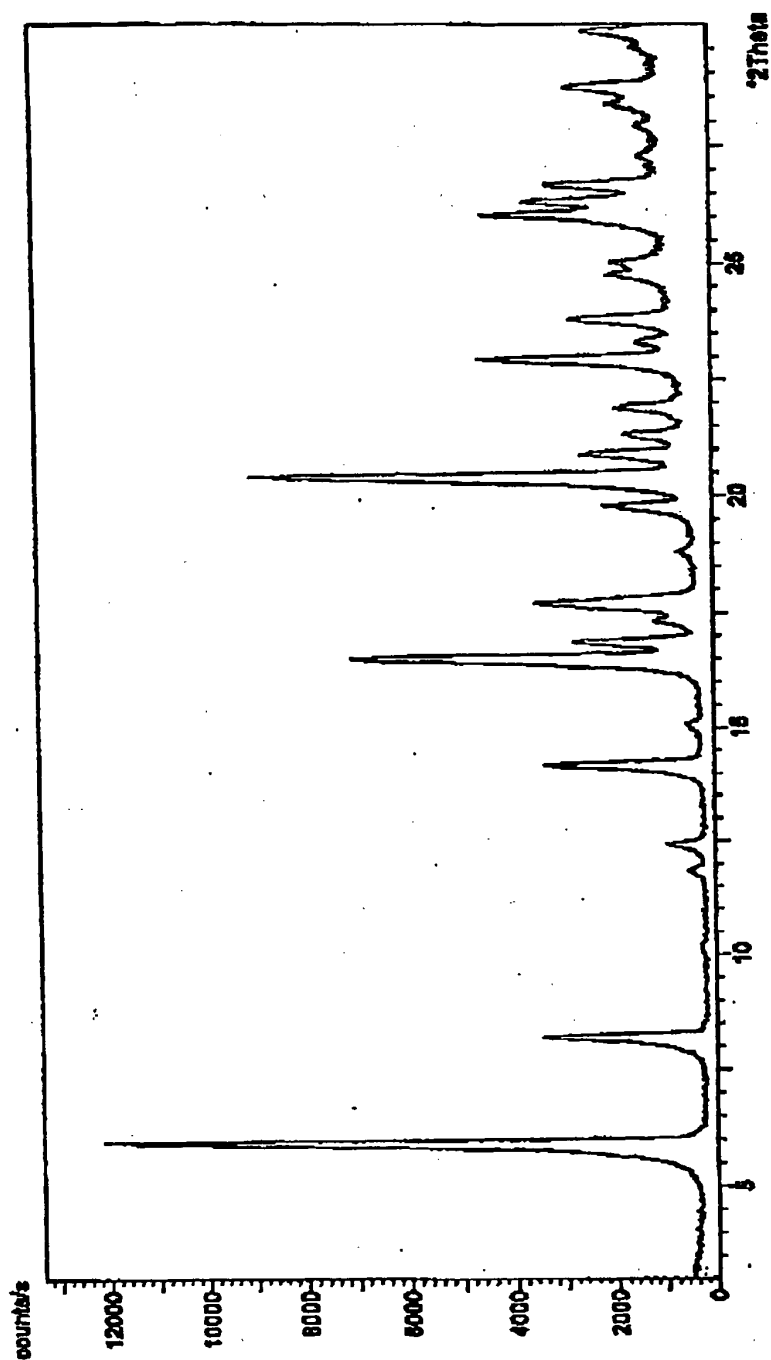
The x-ray diffraction chart of the crystals obtained by Experiment II is shown in Fig. 12. The X-ray diffraction chart of the Neotame crystals obtained by Experiment II (Fig. 12) was then superimposed on the chart of the B-type crystals of Neotame (Fig. 2) for the purpose of comparison with the B-type crystals, as indicated in Fig. 13. As can be seen from Fig. 13, the crystals of Experiment II contain the B-type crystals, as indicated by the appearance of peaks B1, B3, B9, B11, and B12, which are characteristic of the B-type crystals. There were also observed, however, the additional peaks X1 ($2\theta = 5.64$) and X2 ($2\theta = 8.33$), and the relative intensities of these peaks were stronger than that in Experiment I, and therefore, the crystals are probably mixed with some unknown type crystal in a larger amount than the crystals of Experiment I.

The x-ray diffraction chart of the Neotame crystal obtained by Experiment II (Fig. 12) was also superimposed on the chart of the A-type crystals of Neotame (Fig. 1) for the purpose of comparison with the A-type crystals, as indicated in Fig. 14. As can be seen from Fig. 14, none of the four peaks A1, A2, A5, and A15 selected by the present inventors as being characteristic of the A-type crystals are observed on the chart of the crystal of Experiment II.

In conclusion, repetition of Example 2 of Claude et al with maintaining the temperature of the solution at a temperature of not lower than 30°C during concentration gives a mixture of the B-type crystals and some unknown type crystal, and does not afford A-type crystals.

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FIGURE 1



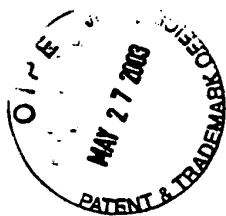


FIGURE 2

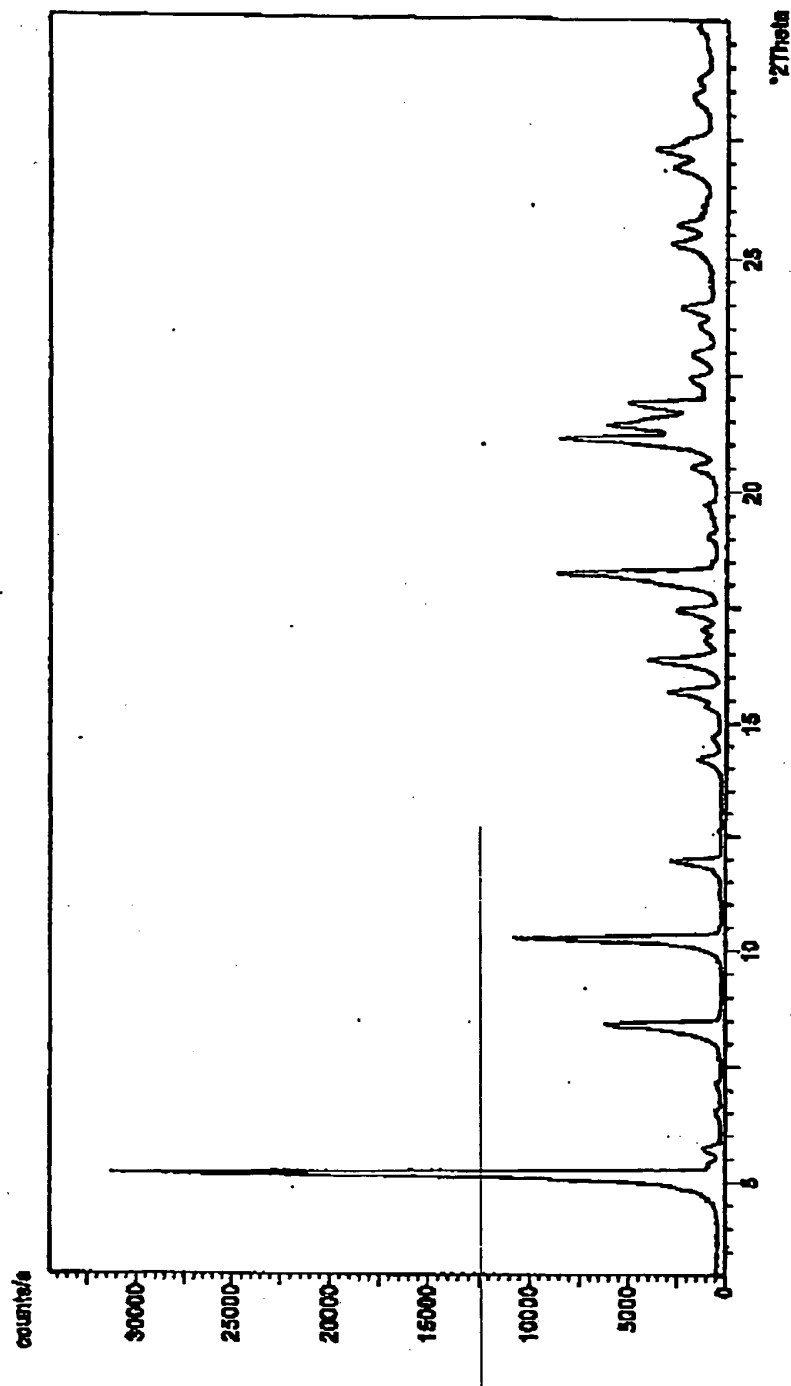


FIGURE 3

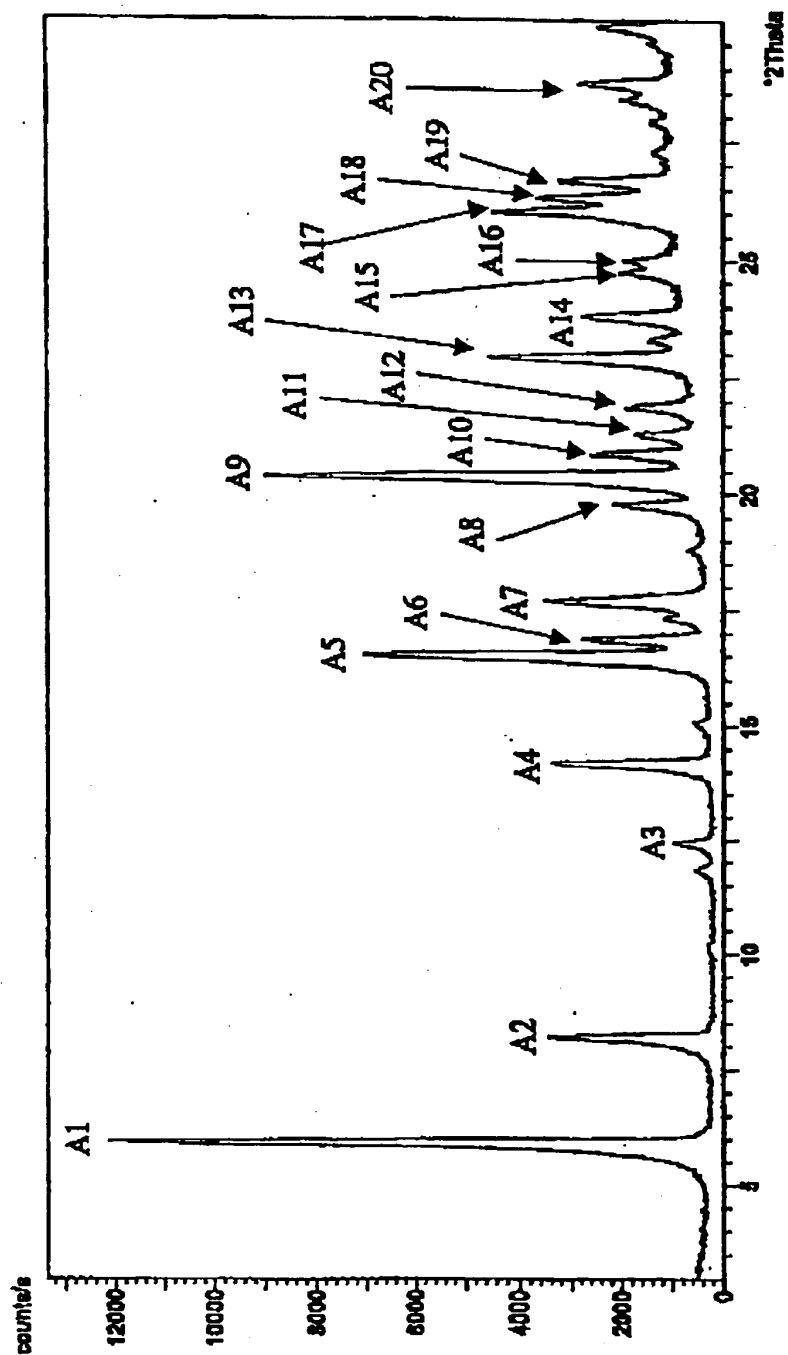
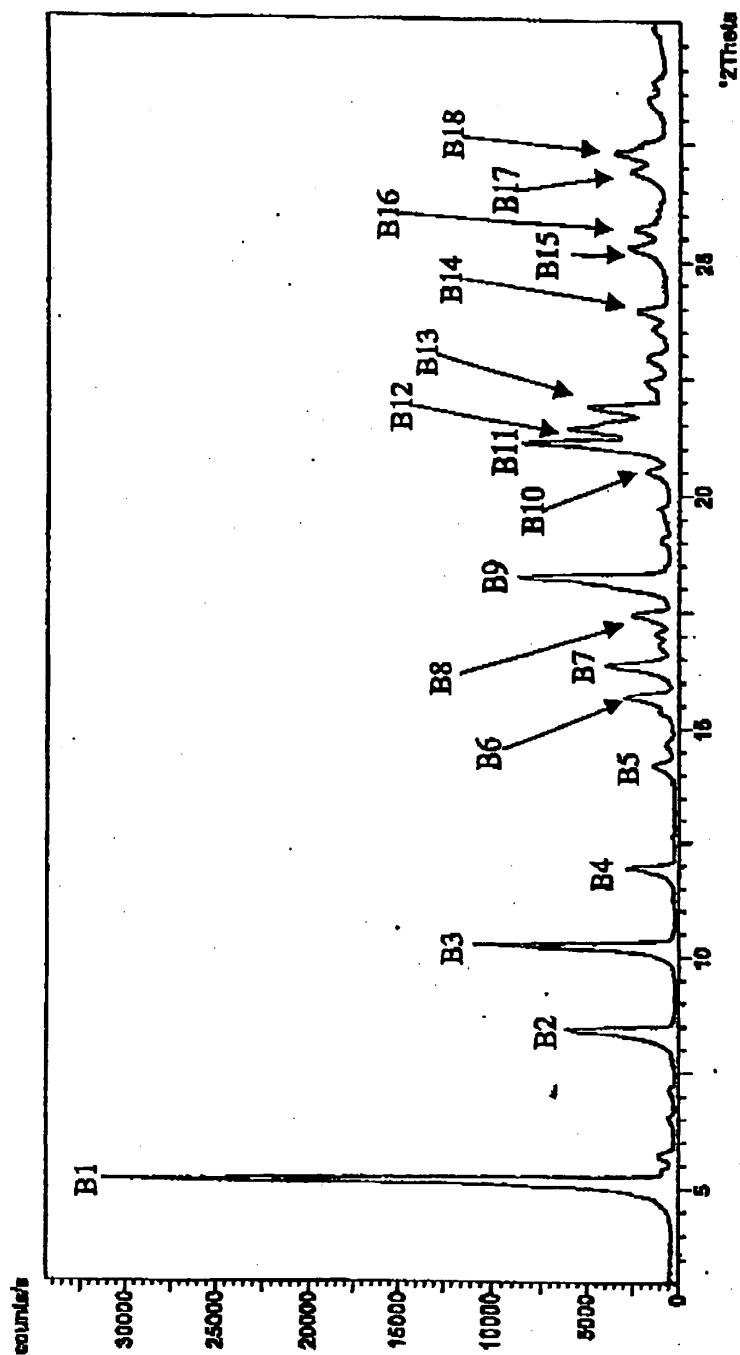
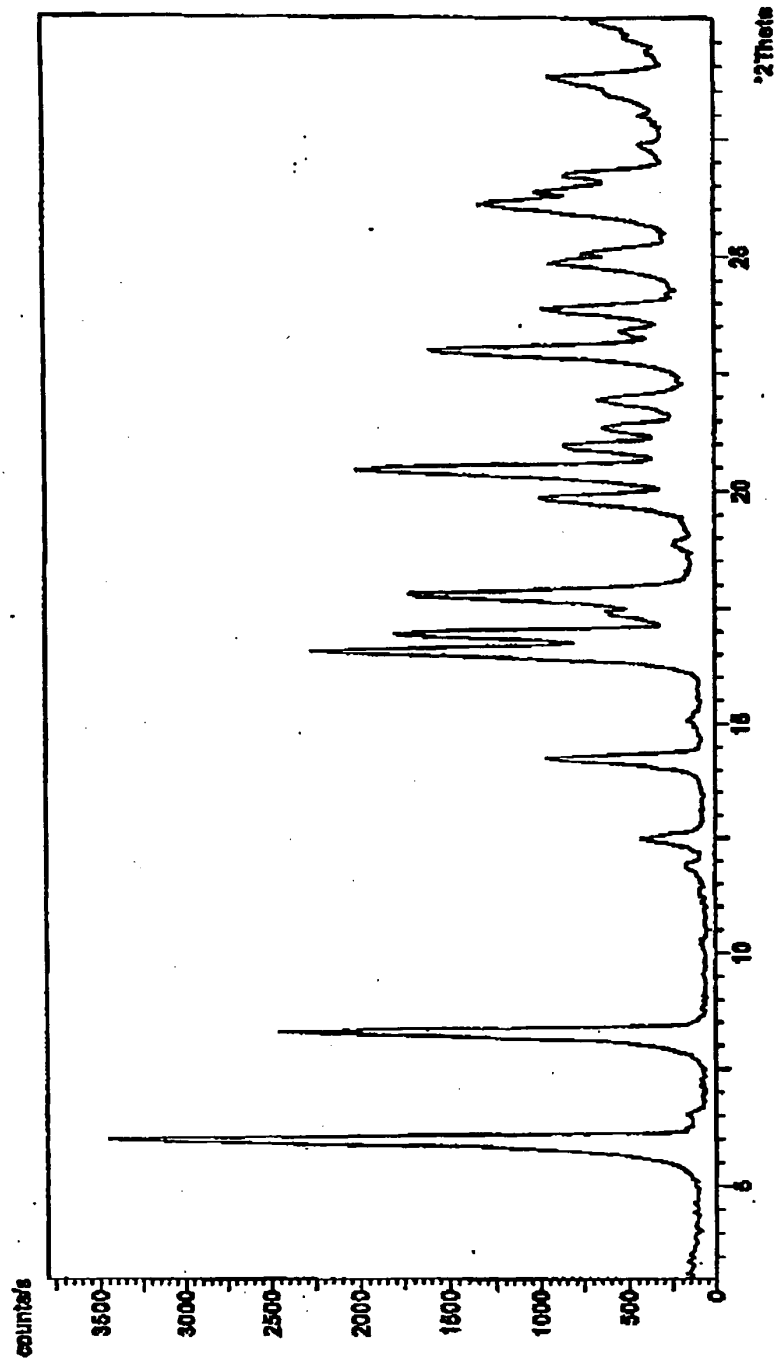


FIGURE 4



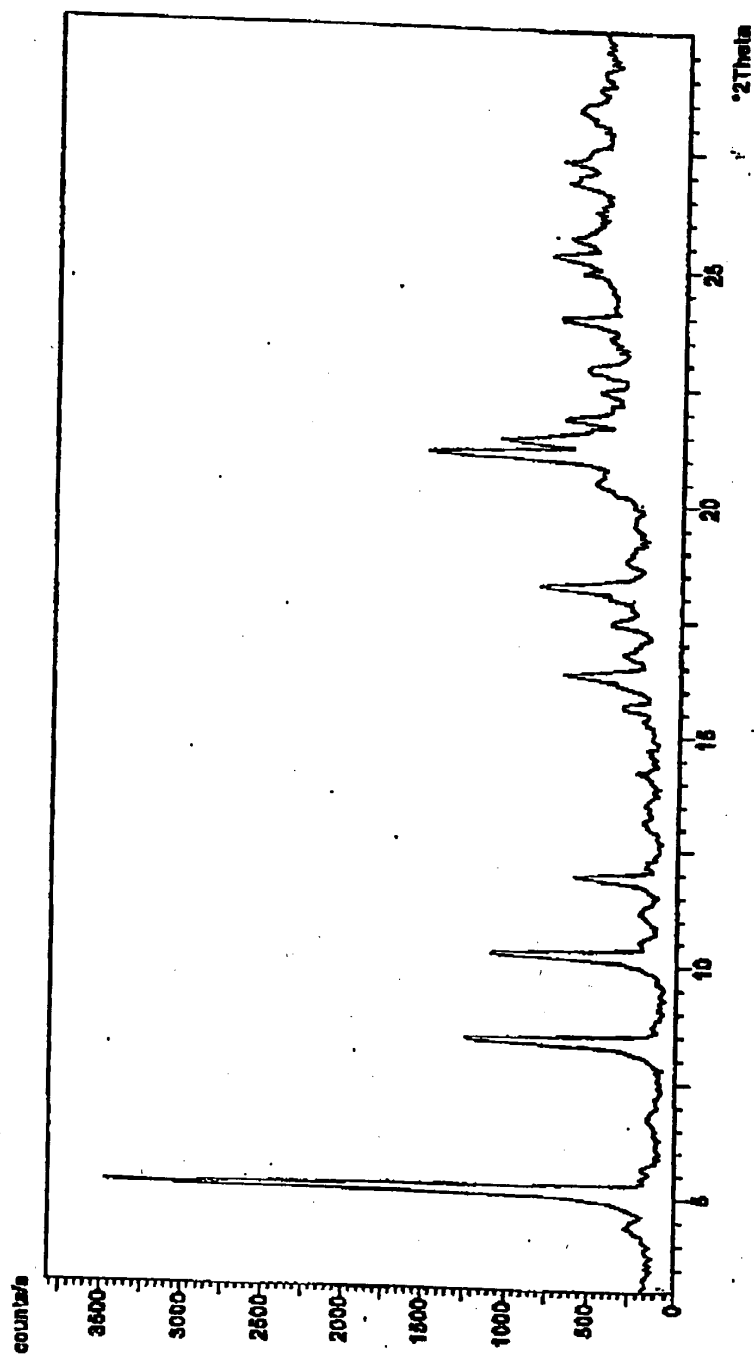
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FIGURE 5



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FIGURE 6



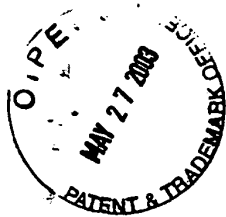


FIGURE 7

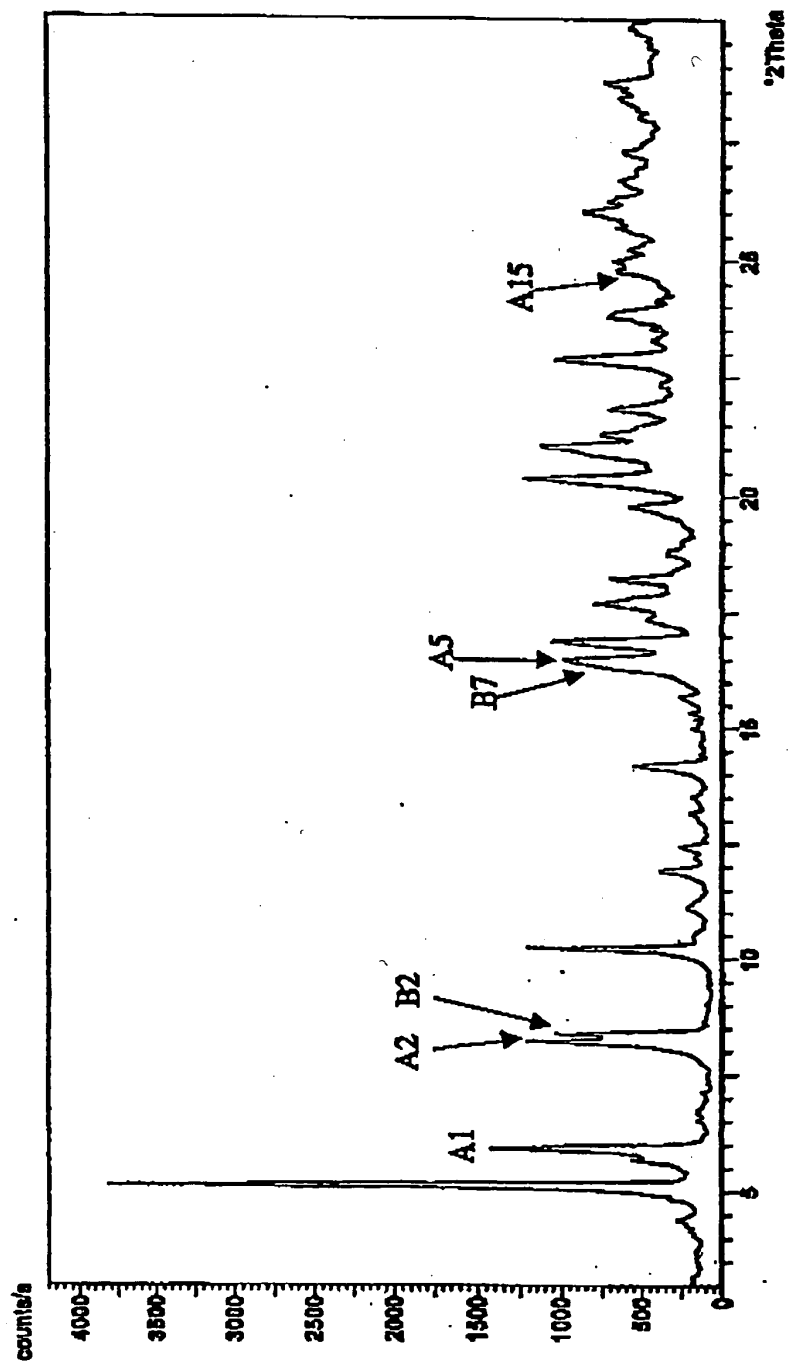
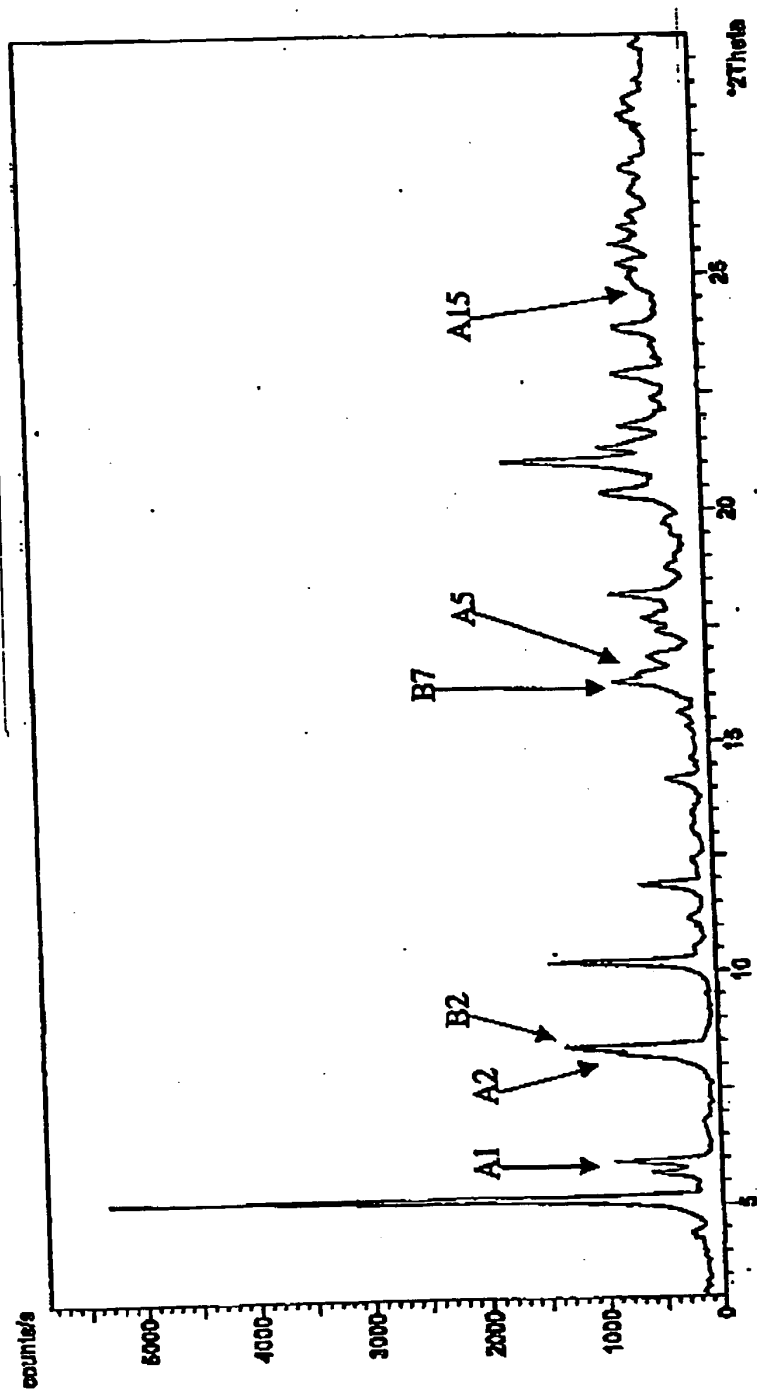


FIGURE 8



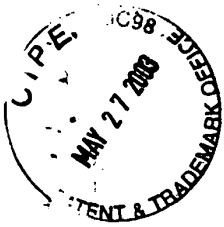


FIGURE 9

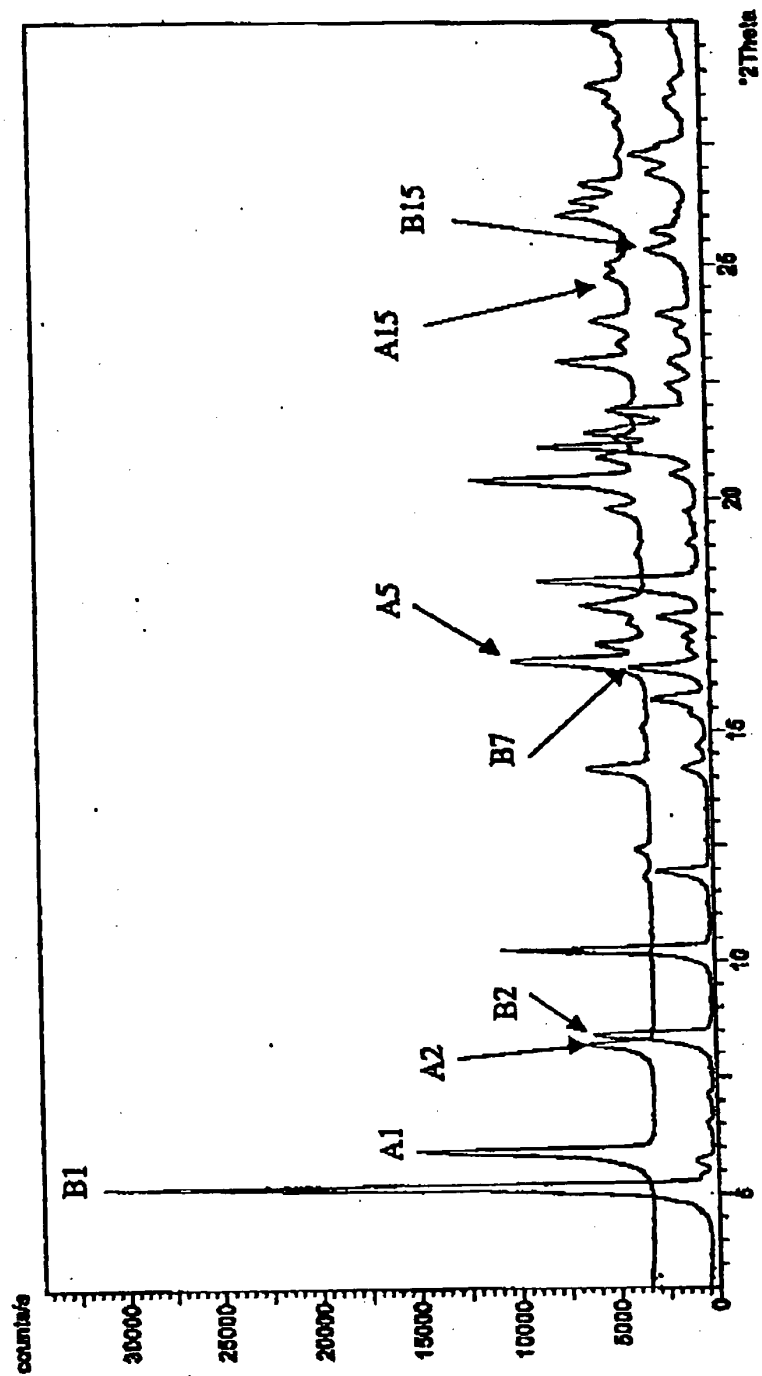




FIGURE 10

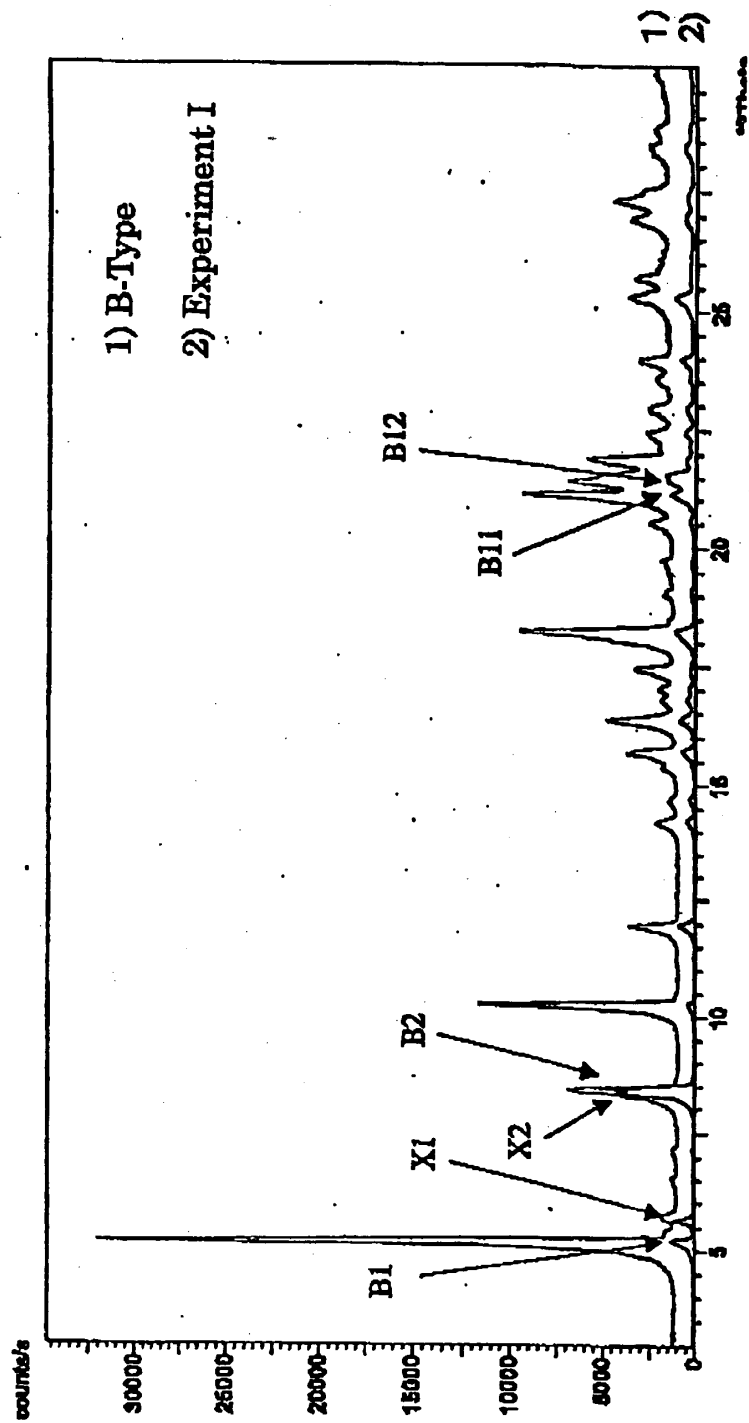
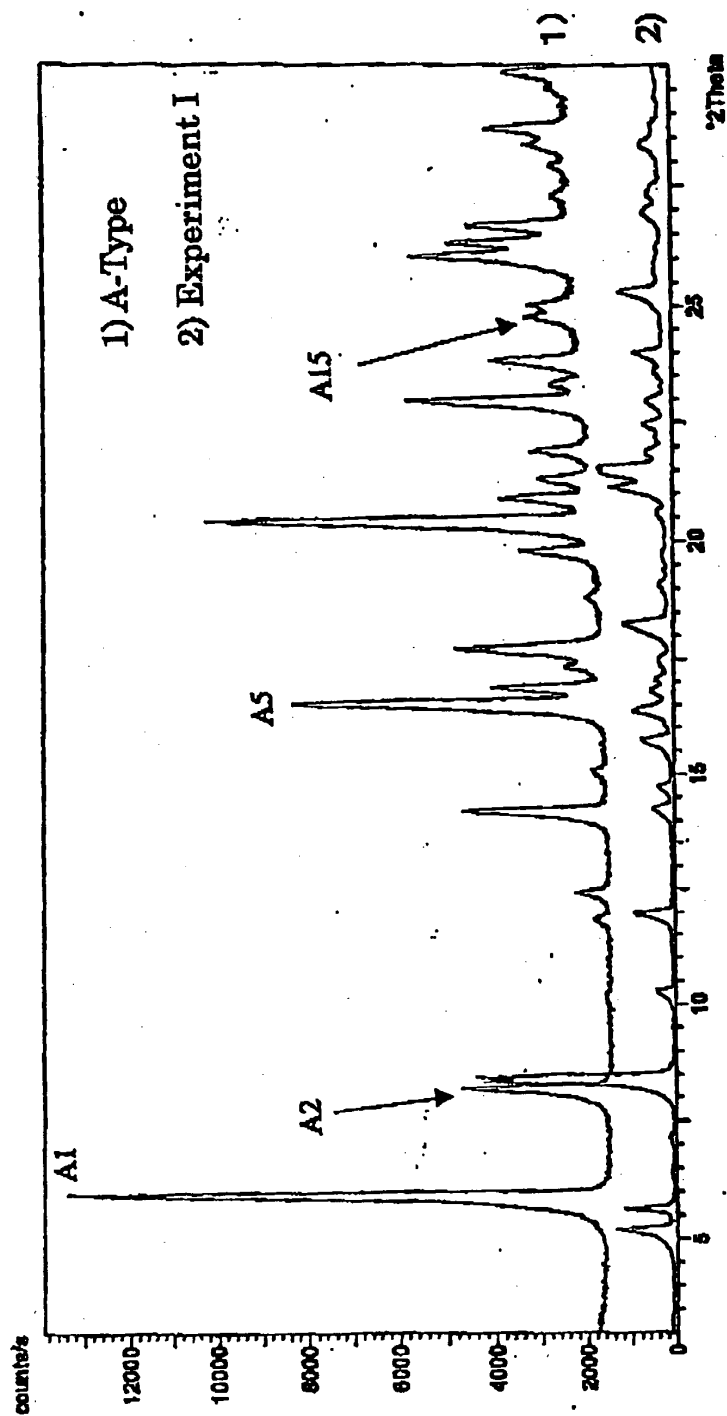


FIGURE 11



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FIGURE 12

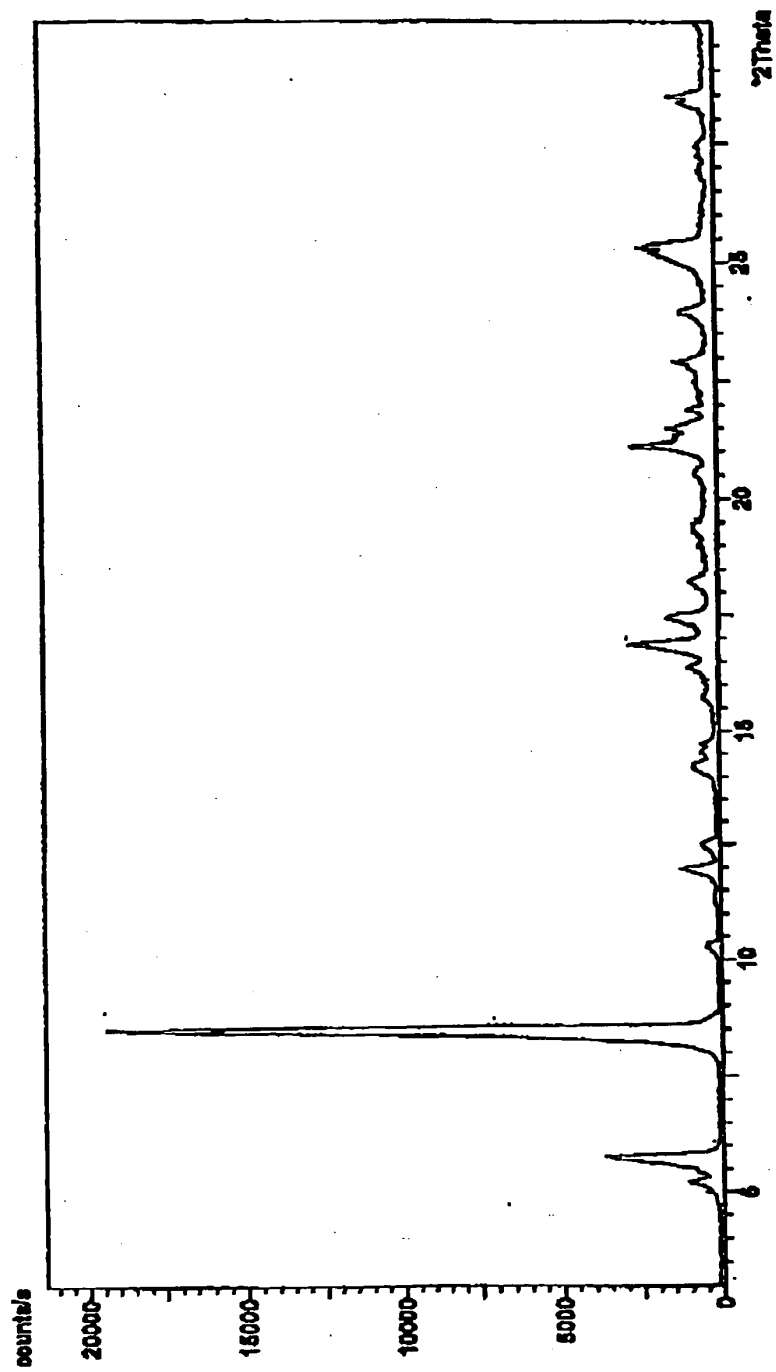




FIGURE 13

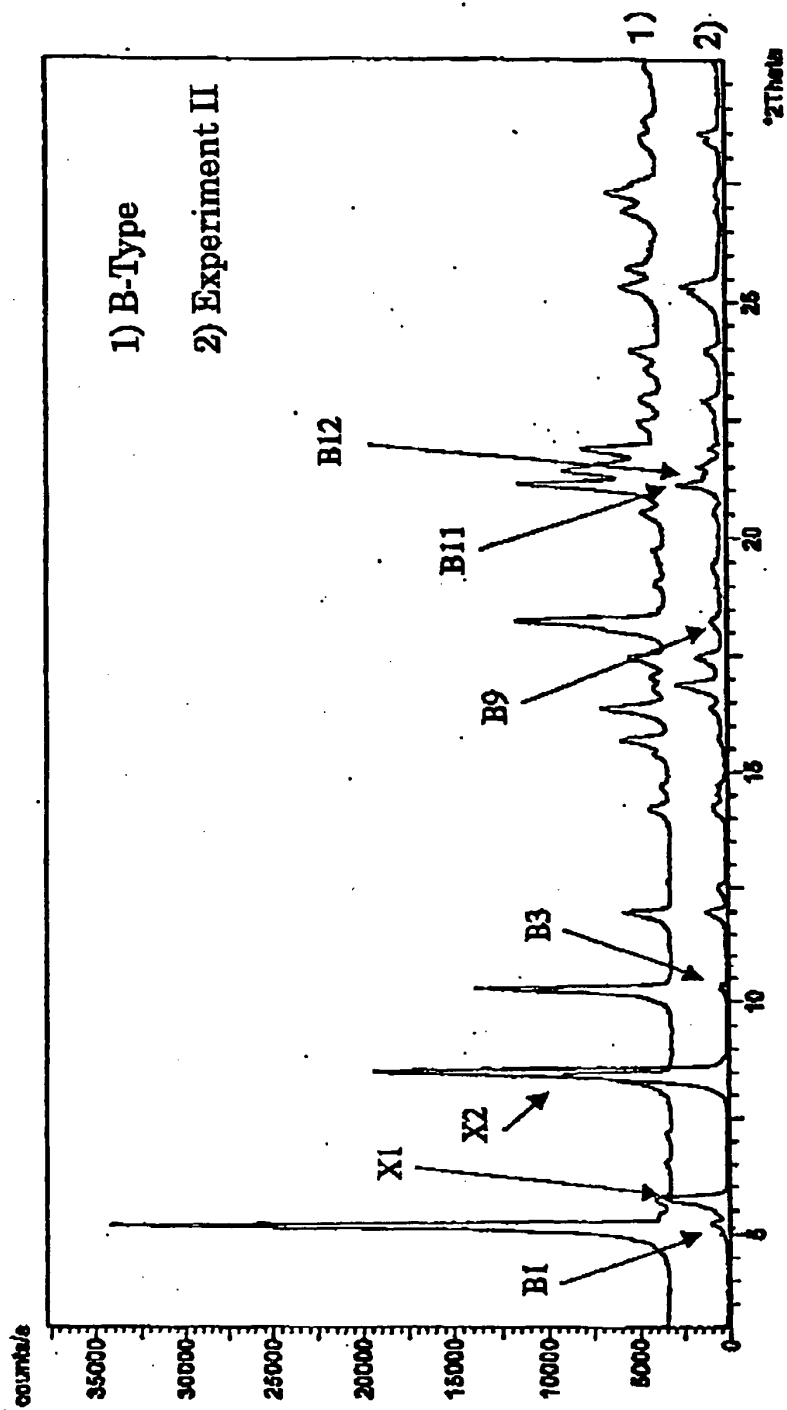
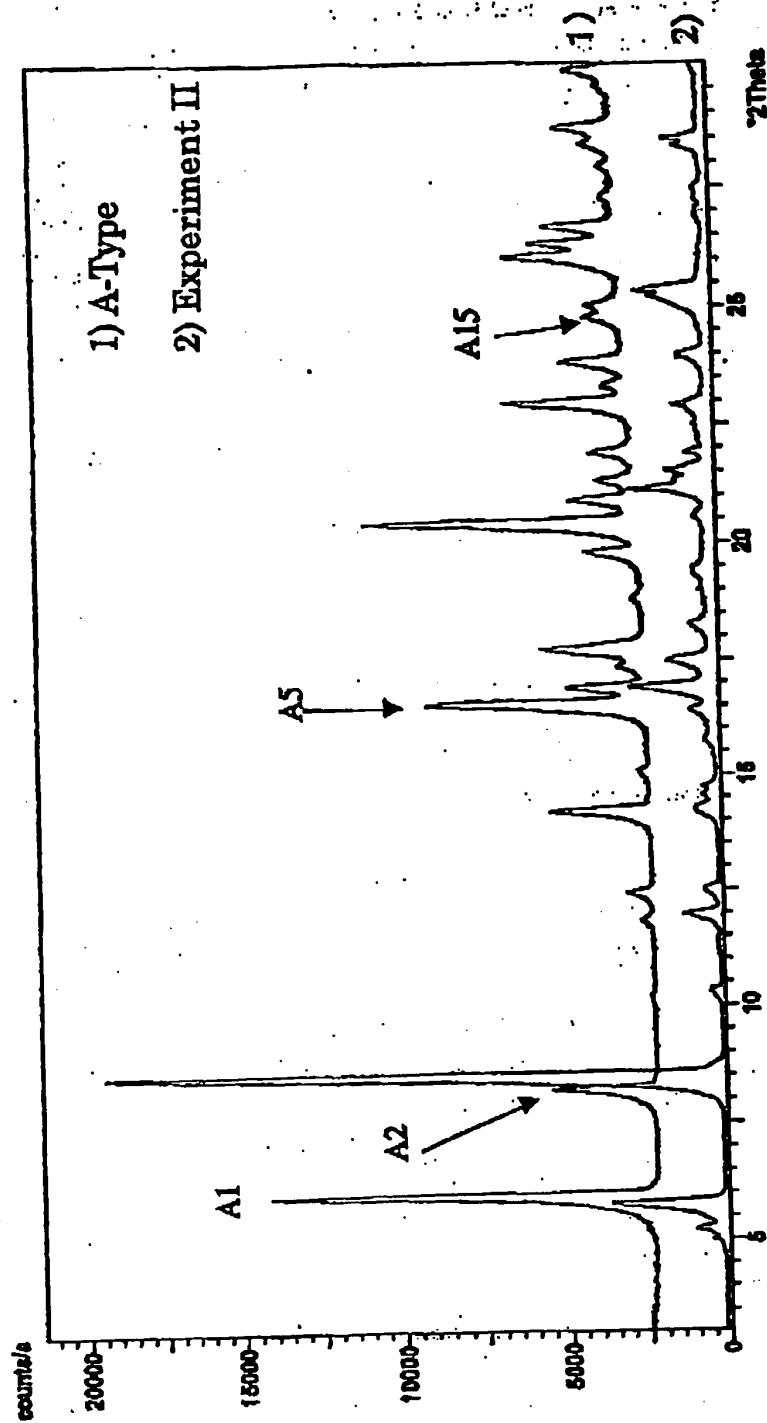


FIGURE 14



13. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

14. Further Declarant saith not.

Shigeru Kawahara
Shigeru Kawahara

April 22, 2003
Date

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